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ORIGINAL REPORT

Intestinal Obstruction in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
For adult survivors of childhood cancer, knowledge about the long-term risk of intestinal obstruction from surgery, chemotherapy, and radiotherapy is limited.

Methods
Intestinal obstruction requiring surgery (IOS) occurring 5 or more years after cancer diagnosis was evaluated in 12,316 5-year survivors in the Childhood Cancer Survivor Study (2,002 with and 10,314 without abdominopelvic tumors) and 4,023 sibling participants. Cumulative incidence of IOS was calculated with second malignant neoplasm, late recurrence, and death as competing risks. Using piecewise exponential models, we assessed the associations of clinical and demographic factors with rate of IOS.

Results
Late IOS was reported by 165 survivors (median age at IOS, 19 years; range, 5 to 50 years; median time from diagnosis to IOS, 13 years) and 14 siblings. The cumulative incidence of late IOS at 35 years was 5.8% (95% CI, 4.4% to 7.3%) among survivors with abdominopelvic tumors, 1.0% (95% CI, 0.7% to 1.4%) among those without abdominopelvic tumors, and 0.3% (95% CI, 0.1% to 0.5%) among siblings. Among survivors, abdominopelvic tumor (adjusted rate ratio [ARR], 3.6; 95% CI, 1.9 to 6.8; $P < .001$) and abdominal/pelvic radiotherapy within 5 years of cancer diagnosis (ARR, 2.4; 95% CI, 1.6 to 3.7; $P < .001$) increased the rate of late IOS, adjusting for diagnosis year; sex; race/ethnicity; age at diagnosis; age during follow-up (as natural cubic spline); cancer type; and chemotherapy, radiotherapy, and surgery within 5 years of cancer diagnosis. Developing late IOS increased subsequent mortality among survivors (ARR, 1.8; 95% CI, 1.1 to 2.9; $P = .016$), adjusting for the same factors.

Conclusion
The long-term risk of IOS and its association with subsequent mortality underscore the need to promote awareness of this complication among patients and providers.

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INTRODUCTION

Children who survive cancer are at risk of developing GI complications in the years and decades after diagnosis.[1] Survivors of childhood cancer may be at increased risk of intestinal obstruction as a sequela of surgery, chemotherapy, and/or radiotherapy. However, no study to date has rigorously investigated the occurrence of intestinal obstruction in this population. As 5-year overall survival rates of all major childhood cancers have increased over the last few decades, recognizing the long-term effects of therapy has become increasingly important.[2,3] Using the large population of the Childhood Cancer Survivor Study (CCSS), we sought to define the incidence of and identify risk factors for late-occurring intestinal obstruction requiring surgery (IOS) after a primary diagnosis of childhood cancer.

METHODS

Population

We included 12,316 survivors of childhood cancer and 4,023 siblings of survivors from CCSS, a retrospective cohort study with ongoing, longitudinal follow-up of survivors diagnosed with leukemia, lymphoma, Wilms tumors, neuroblastoma, soft tissue sarcoma, bone tumors, or malignant CNS tumors before age 21 years. Hepatic tumors and non-CNS germ cell tumors were not included in CCSS. Survivors were diagnosed between January 1, 1970, and December 31, 1986, at one of 26 participating

institutions in the United States or Canada and survived at least 5 years from diagnosis. Nearest-age siblings of a random subset of survivors were recruited as a comparison population. Further details of CCSS study methodology have been previously published.[4-6]

Predictors and Covariates

Data were abstracted from participant responses to baseline (initiated in 1994) and follow-up questionnaires (2000, 2003, and 2007). In the baseline questionnaire, participants provided demographic characteristics. International Classification of Diseases for Oncology topography codes were used to identify patients with tumors in the abdomen, pelvis, or retroperitoneum. Tumors located in the thoracic or lumbar spine were not considered abdominopelvic tumors. Survivors who underwent abdominal and/or pelvic surgery within the first 5 years of diagnosis were identified based on International Classification of Diseases, Ninth Revision, Clinical Modification procedure codes abstracted from participating institutions' medical records. Surgical procedures were also obtained from the baseline and follow-up questionnaires.

Chemotherapy and radiotherapy exposure was systematically obtained from the medical records of participating hospitals and institutions, based on a standardized protocol.[4] Chemotherapy data included all treatments within 5 years of the primary cancer diagnosis. Chemotherapy was assessed both as a binary variable (did or did not receive chemotherapy) and as a categorical variable (type of chemotherapy agent). In addition, an alkylating agent score (cyclophosphamide equivalent dose) and a platinum agent score were calculated based on previously published formulas, which estimate cumulative exposure to these agents.[7-9] Radiotherapy data were collected and analyzed in collaboration with the Radiation Physics Center at The University of Texas MD Anderson Cancer Center.[10] Radiotherapy directed to the abdomen and/or pelvis occurring within 5 years of childhood cancer diagnosis was assessed as both a binary variable (did or did not receive radiotherapy directed to the abdomen and/or pelvis) and as a continuous variable (maximum total dose). Maximum total dose reflects maximum cumulative dose directed to any part of the abdomen and/or pelvis within the first 5 years after diagnosis of the primary tumor.

Outcomes

The primary outcome was late IOS occurring 5 or more years after childhood cancer diagnosis. IOS was defined by an affirmative participant response to the questionnaire item "Please indicate if you have ever had surgery for intestinal obstruction (blocked intestines)" on baseline or follow-up surveys. Time to IOS was calculated as the difference between reported age at IOS and age at initial diagnosis. Multiple imputation[11] for the age at event was used for patients among whom IOS was reported but the year or age at which the participant underwent surgery was unknown (survivors with abdominopelvic tumors, n = 28; survivors without abdominopelvic tumors, n = 10). Briefly, 10 imputed data sets were created, and all analyses were performed on each. Rubin's rules were used to combine the results.[12] All-cause mortality was assessed as a secondary outcome. Time to death was calculated as the difference between date of death and date of cohort entry (ie, 5 years after childhood cancer diagnosis). IOS was treated as a time-dependent variable.

Prevalence of early IOS (ie, within 5 years of diagnosis) was calculated to better characterize the primary end point of IOS before eligibility for CCSS. Patients who did not survive until 5 years after diagnosis were not eligible for CCSS and were not included in prevalence estimations. For the main analysis of late-onset obstruction, because CCSS did not capture recurrent IOS events, survivors with early IOS within 5 years of diagnosis were not included. The primary end point of late-occurring IOS reflects only IOS occurring 5 or more years from diagnosis and does not include early IOS.

Statistical Analysis

For initial unadjusted analyses, categorical covariates were compared between survivors with and without abdominopelvic tumors using the χ^2 test. Cumulative incidence (with 95% CIs) of late IOS (ie, > 5 years since diagnosis) was calculated for each of the following three groups: survivors with abdominopelvic tumors, survivors without abdominopelvic tumors, and siblings. Follow-up time began with time of entry into the cohort (ie, 5 years after childhood cancer diagnosis); for the siblings, their corresponding survivors' cohort entry dates were used. Follow-up ended at the earliest occurrence of the following events: late IOS, second malignant neoplasm, late recurrence, or death. The latter three events (second malignant neoplasm, late recurrence, and death) were considered competing risk events. Analyses restricted to survivors (excluding siblings) used piecewise exponential models[13-15] to compare the rate of late IOS between survivors with and without abdominopelvic primary cancers, adjusting for the following factors: year of diagnosis, sex, race/ethnicity, age at diagnosis, primary cancer type, and prior chemotherapy, radiotherapy, and/or surgery within 5 years after cancer diagnosis. Person-time was partitioned by age during follow-up, divided into 1-year increments, and included in the model in the form of natural cubic splines to allow the model to have a nonconstant baseline rate. We considered the prevalence at the study entry for having experienced IOS in the first 5 years after diagnosis among survivors and siblings. Prevalence ratios at 5 years after diagnosis were estimated using generalized linear models with a long-link function along with generalized estimating equations to account for with-family correlation, adjusting for age, sex, and race/ethnicity. Piecewise exponential models were also used to compare mortality between survivors who did and did not experience IOS, with IOS as a time-dependent variable, adjusting for the same factors as mentioned earlier. Statistical analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC) and R Version 2.15.1 (www.r-project.org).

RESULTS

Overall Cohort

Table 1 lists baseline demographic and treatment information for survivors and siblings. Among 12,316 survivors, 2,002 survivors had abdominopelvic tumors (lymphoma, neuroblastoma, Wilms tumors, bone tumors, and soft tissue sarcomas) and 10,314 survivors did not. The most common primary cancer diagnoses among survivors with abdominopelvic tumors were Wilms tumors (60%, n = 1,204) and neuroblastoma (23%, n = 457). The most common primary diagnoses among survivors who did not have abdominopelvic tumors were leukemia (46%, n = 4,698) and CNS malignancies (18%, n = 1,869). In addition, 4,023 siblings of survivors were included for comparison. Information about missing demographic and treatment variables can be found in Appendix Table A1 (online only).

The majority of survivors with abdominopelvic tumors had undergone one or more abdominal or pelvic surgeries in the first 5 years after cancer diagnosis (77%, n = 1,323), whereas most survivors without abdominopelvic tumors had not (90%, n = 8,169). Multiple abdominal or pelvic surgeries were common among patients with abdominopelvic tumors, with 32% (n = 550) undergoing one surgery, 23% (n = 405) undergoing two surgeries, and 21% (n = 368) undergoing three or more surgeries in the first 5 years after cancer diagnosis. Most survivors received chemotherapy in the first 5 years after diagnosis (90% of those with and 79% of those without abdominopelvic tumors). More than half of survivors with abdominopelvic tumors received radiotherapy directed to the abdomen or pelvis (57%, n = 978), whereas few survivors without abdominopelvic tumors received this treatment (18%, n = 1,614).

As displayed in Figures 1A to 1C, the cumulative incidence of late-occurring IOS at 35 years since the childhood cancer diagnosis was 5.8% (95% CI, 4.4% to 7.3%), 1.0% (95% CI, 0.7% to 1.4%), and 0.3% (95% CI, 0.1% to 0.5%) for survivors of abdominopelvic tumors, survivors without an abdominopelvic tumor, and siblings, respectively. Characteristics of late IOS are listed in Table 2. Survivors

Table 1. Demographic and Treatment Characteristics of 12,316 Survivors of Childhood Cancer and 4,023 Siblings

Characteristic	No. (%)*		
	Abdominopelvic Tumor (n = 2,002)	No Abdominopelvic Tumor (n = 10,314)	Siblings (n = 4,023)
Primary cancer			
CNS	0 (0)	1,869 (18)	
Leukemia	0 (0)	4,698 (46)	
Lymphoma	146 (7)	1,336 (13)	
Wilms tumor	1,204 (60)	0 (0)	
Neuroblastoma	457 (23)	378 (4)	
Bone tumor	18 (1)	1,115 (11)	
Soft tissue sarcoma	177 (9)	918 (9)	
No. of abdominal/pelvic surgeries†			
0 (no surgery)	401 (23)	8,169 (90)	
1	550 (32)	223 (2)	
2	405 (23)	241 (3)	
≥ 3	368 (21)	446 (5)	
Received chemotherapy†			
Yes	1,547 (90)	7,169 (79)	
No	178 (10)	1,923 (21)	
Alkylating agent CED, mg/m^2†			
0	1,132 (69)	4,309 (52)	
1-3,999	92 (6)	1,098 (13)	
4,000-7,999	129 (8)	895 (11)	
≥ 8,000	286 (17)	1,918 (23)	
Platinum agent score†			
1	37 (44)	168 (38)	
2	13 (15)	92 (21)	
3	35 (41)	187 (42)	
Dose to abdomen/pelvis from all radiotherapy, Gy†			
0 (no radiotherapy)	726 (43)	7,306 (82)	
< 10	22 (1)	50 (1)	
10-19	205 (12)	238 (3)	
20-29	393 (23)	372 (4)	
30-39	216 (13)	499 (6)	
40-49	96 (6)	325 (4)	
≥ 50	46 (3)	123 (1)	
Sex			
Male	995 (50)	5,540 (54)	1,937 (48)
Female	1,007 (50)	4,774 (46)	2,086 (52)
Race/ethnicity			
Non-Hispanic white	1,691 (85)	8,915 (86)	3,509 (87)
Non-Hispanic black	158 (8)	431 (4)	112 (3)
Hispanic	96 (5)	582 (6)	148 (4)
Other	57 (3)	386 (4)	254 (6)
Year of diagnosis			
1970-1974	351 (18)	1,781 (17)	
1975-1979	556 (28)	2,928 (28)	
1980-1986	1,095 (55)	5,605 (54)	
Age at diagnosis, years			
0-3	1,252 (63)	3,071 (30)	
4-9	550 (27)	3,273 (32)	
10-14	128 (6)	2,153 (21)	
15-20	72 (4)	1,817 (18)	

Abbreviation: CED, cyclophosphamide equivalent dose.
*Percentages are column percentages, where the denominator is the total number of patients for whom treatment exposure or demographic characteristics were ascertained.
†Occurring within 5 years of childhood cancer diagnosis.

with abdominopelvic tumors experienced late IOS at a younger median age (16 years; interquartile range, 11 to 22 years) compared with survivors without abdominopelvic tumors (median age, 23 years; range, 17 to 31 years) and siblings (median age, 33 years; range, 13 to 36 years). There was no association between chemotherapy, cyclophosphamide equivalent dose, or platinum agent score and late IOS. Among all survivors, abdominal tumor (adjusted rate ratio [ARR], 3.6; 95% CI, 1.9 to 6.8; $P < .001$) and prior abdominal/pelvic radiotherapy (ARR, 2.4; 95% CI, 1.6 to 3.7; $P < .001$) were associated with increased rates of IOS. Figure 2 displays the cumulative incidences of late IOS for patients with and without abdominopelvic tumors and with and without abdominal/pelvic radiotherapy.

Survivors With Abdominopelvic Tumors

Among survivors with abdominopelvic tumors who had late IOS, the overall median time from diagnosis to the first late IOS was 12 years (interquartile range, 8 to 19 years). In this group, survivors of lymphoma had the highest cumulative incidence of late-occurring IOS, with a cumulative incidence of 7.2% at 35 years from diagnosis. Radiotherapy was significantly associated with late IOS (ARR, 2.3; 95% CI, 1.3 to 4.0; $P = .004$). Survivors with abdominopelvic tumors who received abdominal/pelvic radiotherapy were at higher risk of late IOS compared with survivors treated without abdominal/pelvic radiotherapy and survivors without abdominopelvic tumors (Fig 2). Furthermore, compared with those with no abdominal/pelvic radiotherapy, late IOS was more likely with increasing abdominal/pelvic radiotherapy doses. Table 3 lists further details of the multivariable analysis of factors associated with late IOS among survivors with abdominopelvic tumors. Multivariable analyses were similar with and without inclusion of primary cancer diagnosis (Appendix Table A1, online only).

Survivors Without Abdominopelvic Tumors

Among survivors without abdominopelvic tumors who developed late IOS, the overall median time from diagnosis to the first late IOS was 15 years (interquartile range, 9 to 21 years). Within this group of survivors, those with leukemia were least likely to have late-occurring IOS (0.6% at 35 years after diagnosis). In the multivariable analysis of survivors without abdominopelvic tumors (Table 3), prior abdominal or pelvic surgery and abdominal/pelvic radiotherapy doses greater than 50 Gy significantly increased the rate of late-occurring IOS. Analysis excluding primary cancer diagnosis was similar (Appendix Table A2). Age at diagnosis was inversely associated with late-occurring IOS.

Early Outcomes

The prevalence of IOS within 5 years of diagnosis was 1.6% and 0.1% for survivors and siblings, respectively. For survivors with and without abdominopelvic tumors, the prevalence of IOS within 5 years of diagnosis was 6.9% and 0.5%, respectively. The prevalence ratios of IOS (with siblings as the referent group) at 5 years since diagnosis were 8.4 (95% CI, 5.2 to 13.8) for the overall cohort, 47.9 (95% CI, 28.0 to 82.0) for survivors with abdominopelvic tumors, and 3.0 (95% CI, 1.7 to 5.2) for survivors without abdominopelvic tumors.

Mortality Analysis

A total of 1,737 survivors died during the study period, including 162 (8%) with abdominopelvic tumors and 1,575 (15%) without

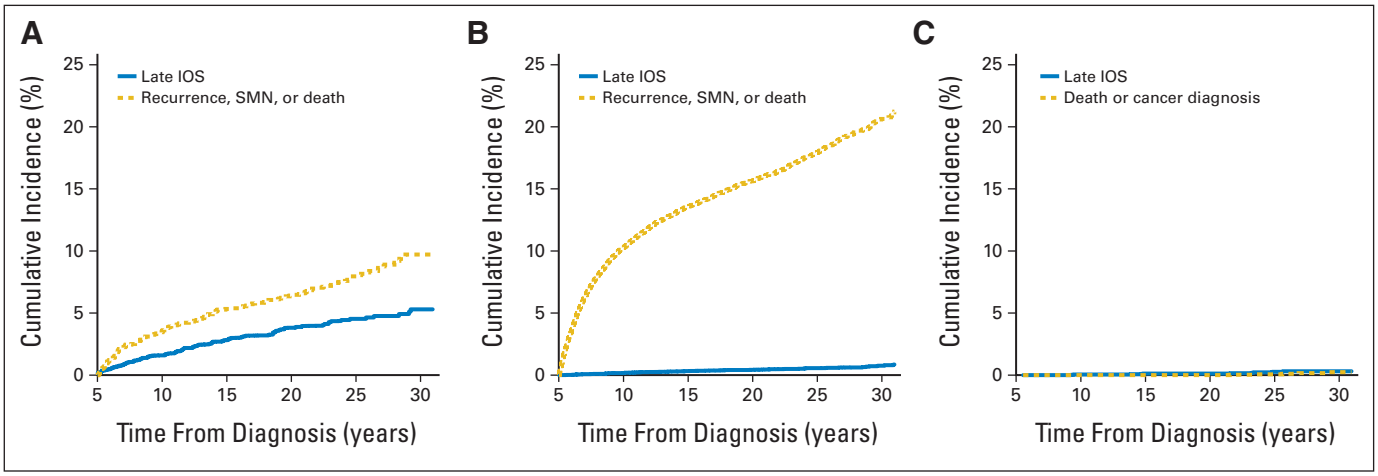

Fig 1. Cumulative incidence of late intestinal obstruction requiring surgery (IOS) at 35 years from diagnosis among (A) survivors with abdominopelvic tumors (5.8%), (B) survivors without abdominopelvic tumors (1.0%), and (C) siblings of survivors (0.3%), treating primary tumor recurrence, subsequent malignant neoplasm (SMN), and death as competing risks.

abdominopelvic tumors. Survivors of childhood cancer who developed late-occurring IOS were at increased risk of mortality (ARR, 1.8; 95% CI, 1.1 to 2.9; $P = .016$), while controlling for potential confounding factors. Details of the association between late IOS and mortality are listed in Table 4.

DISCUSSION

In this large population of survivors of childhood cancer, risk of late-occurring IOS was increased compared with siblings. Elevated risk of IOS was associated with presence of an abdominopelvic tumor and prior exposure to abdominal or pelvic radiotherapy. Among survivors with abdominopelvic tumors, lymphoma resulted in the highest cumulative incidence of late-occurring IOS (7.2% at 35 years after diagnosis).

Existing knowledge about intestinal obstruction in the pediatric oncology population is sparse and largely derives from single-institution, retrospective studies. An analysis by Aguayo et al[16] in 2010 reported that intestinal obstruction (not necessarily requiring surgery) afflicted 3.7% of 291 pediatric patients diagnosed with intra-abdominal Wilms tumor, rhabdomyosarcoma, neuroblastoma, or lymphoma, with a mean follow-up time of 3.6 years. In the National Wilms Tumor Study results published in 1993, Ritchey et al[17] reported that bowel obstruction was independently associated with age less than 6 years, stage III disease, extrarenal vascular involvement, and resection of other organs. More recent work from Paulino et al[18] in 2000 reports a 15-year bowel obstruction prevalence of 17% for 55

Table 2. Late IOS Among Childhood Cancer Survivors and Their Siblings

IOS	No. (%)*		
	Abdominopelvic Tumor (n = 2,002)	No Abdominopelvic Tumor (n = 10,315)	Siblings (n = 4,023)
IOS	99 (5)	66 (1)	14 (1)
Age at IOS, years†			
0-4			2 (14)
5-10	17 (17)	3 (5)	1 (7)
10-19	46 (46)	18 (27)	1 (7)
20-29	27 (27)	25 (38)	2 (14)
30-39	8 (8)	13 (20)	6 (43)
≥ 40	1 (1)	7 (11)	2 (14)
Years from diagnosis to IOS†			
5-10	37 (37)	18 (27)	
10-19	42 (42)	26 (39)	
20-29	19 (19)	16 (24)	
≥ 30	1 (1)	6 (9)	

Abbreviation: IOS, intestinal obstruction requiring surgery.
*Percentages are column percentages, where the denominator is the total number of patients.
†Percentage denominators are the number of patients who had surgery for intestinal obstruction.

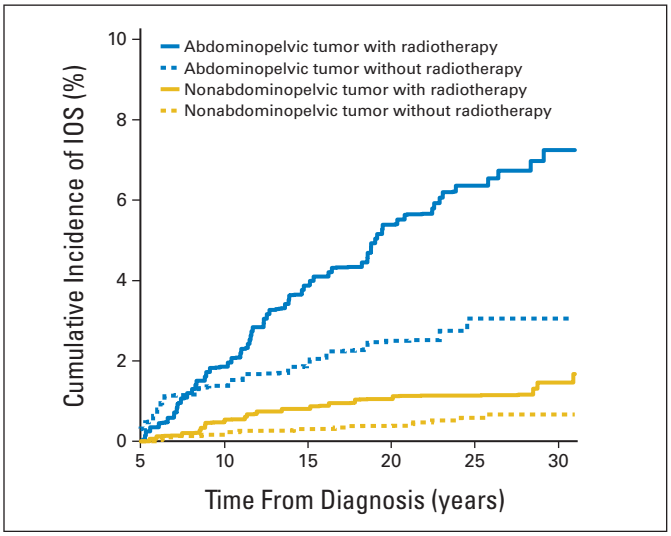

Fig 2. Cumulative incidence of late intestinal obstruction requiring surgery (IOS) among survivors with abdominopelvic tumors who received radiotherapy (7.5%), abdominopelvic tumors who did not receive radiotherapy (3.1%), nonabdominopelvic tumors who received radiotherapy (1.1%), and nonabdominopelvic tumors who did not receive radiotherapy (0.6%), treating primary tumor recurrence, subsequent malignant neoplasm, and death as competing risks (competing risks not displayed).

Table 3. Multivariable Analysis of Factors Associated With Late IOS Among Survivors With and Without Abdominopelvic Tumors

Factor	Abdominopelvic Tumor		No Abdominopelvic Tumor	
	Adjusted Rate Ratio (95% CI)*	*P*	Adjusted Rate Ratio (95% CI)*	*P*
Abdominal/pelvic surgery†				
No	1.0		1.0	
Yes	0.9 (0.5 to 1.4)	.57	4.2 (1.9 to 9.4)	< .001
Chemotherapy†				
No	1.0		1.0	
Yes	0.9 (0.4 to 2.3)	.87	0.8 (0.4 to 1.6)	.54
Dose to abdomen/pelvis from all radiotherapy, Gy†				
0 (no radiotherapy)	1.0		1.0	
< 10	—		3.5 (0.5 to 26.1)	.22
10-19	1.7 (0.7 to 3.8)	.21	—	
20-29	2.2 (1.2 to 4.3)	.014	0.5 (0.1 to 3.9)	.52
30-39	2.6 (1.2 to 5.4)	.012	1.4 (0.5 to 3.9)	.51
40-49	5.2 (2.2 to 12.3)	< .001	2.3 (0.9 to 5.7)	.09
≥ 50	4.1 (0.8 to 19.4)	.08	8.2 (3.0 to 22.2)	< .001
Primary cancer				
CNS	—	—	3.9 (0.5 to 33.0)	.22
Leukemia	—	—	3.4 (0.4 to 27.4)	.26
Lymphoma	1.0 (0.3 to 3.3)	.99	5.6 (0.6 to 48.8)	.12
Wilms tumor	0.9 (0.4 to 1.7)	.66	—	—
Neuroblastoma	1.0		1.0	
Bone tumor	4.6 (0.6 to 33.2)	.13	5.5 (0.6 to 53.8)	.14
Soft tissue sarcoma	0.7 (0.2 to 2.0)	.47	5.6 (0.7 to 46.6)	.11
Sex				
Male	1.0		1.0	
Female	1.0 (0.6 to 1.6)	1.0	1.0 (0.6 to 1.7)	.94
Race/ethnicity				
Non-Hispanic white	1.0		1.0	
Non-Hispanic black	1.0 (0.3 to 2.7)	.94	0.6 (0.1 to 4.7)	.67
Hispanic	0.6 (0.1 to 2.3)	.44	0.3 (0.0 to 2.5)	.28
Other	1.1 (0.3 to 4.6)	.87	0.6 (0.1 to 4.2)	.59
Age at diagnosis, years				
0-3	1.0		1.0	
4-9	1.6 (1.0 to 2.7)	.08	0.5 (0.3 to 1.2)	.13
10-14	0.6 (0.2 to 2.1)	.41	0.3 (0.1 to 0.8)	.022
15-20	0.6 (0.1 to 2.6)	.46	0.5 (0.2 to 1.6)	.26
Year of diagnosis				
1970-1974	1.0		1.0	
1975-1979	1.3 (0.7 to 2.3)	.43	1.4 (0.7 to 3.1)	.36
1980-1986	1.1 (0.6 to 2.1)	.74	1.8 (0.8 to 3.9)	.13

Abbreviation: IOS, intestinal obstruction requiring surgery.
*Adjusted for the variables in the table in addition to age during follow-up as natural cubic splines.
†Occurring within 5 years of childhood cancer diagnosis.

children with Wilms tumor treated with nephrectomy, chemotherapy, and radiotherapy. However, no risk factors were found to be significantly associated with bowel obstruction. Several case reports discuss bowel obstruction after chemotherapy, radiotherapy, or surgery among pediatric patients with lymphoma.[19,20] To date, clear definition of the cumulative incidence of and risk factors for intestinal obstruction among survivors of childhood cancer has not been established.

Although cancer diagnosis is important to acknowledge, risk of IOS is likely more dependent on site and therapy, including surgery and radiotherapy. In our analysis, there was little difference in models for late IOS when primary cancer diagnosis was included (Table 3) and not included (Appendix Table A2). In a 2011 analysis of CCSS data, Goldsby et al[1] document an increased risk of upper and lower GI complications among childhood cancer survivors with prior surgery. In general, surgical resection leads to an increased long-term risk of obstruction, largely caused by intra-abdominal adhesions.[21] After the most common pediatric abdominal procedure performed in the United States, appendectomy,[22] postoperative intestinal obstruction (not necessarily requiring surgery) occurs in 0.2% to 4.5% of patients at a median of 2 to 6 months postoperatively.[23-26] After more extensive abdominal procedures, such as fundoplication, Ladd's procedure, or colectomy, intestinal obstruction requiring operative intervention afflicts 2% to 20% of patients within 9 years after the initial surgery.[27] Data from our study demonstrate that the multimodality treatment of childhood cancer (including surgery) may increase the risk of late-occurring IOS compared with the general, nononcologic pediatric population.

Abdominal or pelvic radiotherapy may lead to increased long-term risk of obstruction as a result of radiation enteritis, with full-thickness

Table 4. Multivariable Analysis of Factors Associated With Mortality Among Survivors

Factor	Adjusted Rate Ratio (95% CI)*	P
Intestinal obstruction requiring surgery†		
No	1.0	
Yes	1.8 (1.1 to 2.9)	.016
Abdominopelvic tumor		
No	1.0	
Yes	0.7 (0.5 to 0.9)	.006
Abdominal/pelvic surgery‡		
No	1.0	
Yes	1.3 (1.1 to 1.5)	.006
Chemotherapy‡		
No	1.0	
Yes	2.0 (1.7 to 2.3)	< .001
Dose to abdomen/pelvis from all radiotherapy, Gy‡		
0 (no radiotherapy)	1.0	
< 10	2.4 (1.4 to 4.1)	.002
10-19	1.6 (1.2 to 2.1)	< .001
20-29	1.3 (1.1 to 1.7)	.008
30-39	1.9 (1.6 to 2.3)	< .001
40-49	2.1 (1.7 to 2.6)	< .001
≥ 50	2.8 (2.2 to 3.7)	< .001
Primary cancer		
Leukemia	1.7 (1.2 to 2.4)	.005
Lymphoma	1.5 (1.0 to 2.1)	.053
Wilms tumor	0.8 (0.5 to 1.2)	.29
Neuroblastoma	1.0	
CNS	3.8 (2.6 to 5.6)	< .001
Bone tumor	1.7 (1.1 to 2.5)	.009
Soft tissue sarcoma	1.8 (1.3 to 2.7)	.001
Sex		
Male	1.0	
Female	0.8 (0.7 to 0.9)	< .001
Race/ethnicity		
Non-Hispanic white	1.0	
Non-Hispanic black	1.4 (1.1 to 1.8)	.018
Hispanic	1.1 (0.9 to 1.4)	.48
Other	1.2 (0.9 to 1.6)	.19
Age at diagnosis, years		
0-3	1.0	
4-9	1.4 (1.2 to 1.7)	< .001
10-14	2.2 (1.8 to 2.7)	< .001
15-20	2.9 (2.4 to 3.6)	< .001
Year of diagnosis		
1970-1974	1.0	
1975-1979	0.8 (0.7 to 0.9)	< .001
1980-1986	0.8 (0.7 to 0.9)	< .001

*Adjusted for the variables in the table in addition to age during follow-up as natural cubic splines.
†Time-dependent variable.
‡Occurring within 5 years of childhood cancer diagnosis.

damage to the bowel wall and subsequent fibrosis.[28,29] A 2010 systematic review by Bolling et al[21] noted insufficient data on late GI complications after radiotherapy in the pediatric oncology population. Work from the National Wilms Tumor Study-3 found an elevated but statistically nonsignificant, rate of bowel obstruction among patients who received higher doses of radiotherapy.[17] A previous report from CCSS found that abdominal radiotherapy increased the risk of upper and lower GI complications.[1] In the present analysis, we report an association between prior radiotherapy and IOS, especially with increasing radiotherapy doses.

Chemotherapy confers known short- and long-term GI toxicities[30]; however, it remains unknown whether chemotherapy affects the risk of obstruction. Although Goldsby et al[1] documented an association between chemotherapy and GI complications, we did not find a convincing association between chemotherapy and IOS in the overall cohort.

Information regarding intestinal obstruction is of particular importance given the severity of its sequelae in this at-risk population of survivors of childhood cancer. In one national study, more than 80% of children with adhesive small bowel obstruction underwent operative intervention with either adhesiolysis or small bowel resection.[31] Mortality associated with small bowel obstruction is as high as 6%.[27] Furthermore, for patients requiring surgery for the treatment of intestinal obstruction, the rate of morbidity (including abscess, fistula, dehiscence, incisional hernia, and pneumonia) has been reported to be higher than 20%.[26] In our analysis, IOS was independently associated with an 80% increase in mortality.

The mechanism for intestinal obstruction among survivors of childhood cancer in this study is unknown, but adhesions from surgery may play a substantive role. Currently, there are no established measures for screening or prevention of postoperative intraperitoneal adhesion formation. Screening is especially challenging because the presence of adhesions is necessary but not sufficient for adhesive bowel obstruction. Compared with laparotomy, the laparoscopic approach has been shown to result in decreased adhesion formation,[32] although minimally invasive techniques may not be feasible in the oncologic setting. There has been some evidence in support of adhesion barriers for the prevention of adhesive bowel obstruction in certain situations.[33] However, given the lack of a clearly effective prophylaxis against intraperitoneal adhesions, the most important measure may be early recognition of intestinal obstruction via education of patients and providers.

Education of primary care physicians, oncologists, surgeons, patients, and patient families is especially important because of the unpredictable occurrence of intestinal obstruction. Specifically, knowledge of the pertinent signs and symptoms (eg, nausea, abdominal distension, obstipation) is paramount. Yet preoperative discussion often does not include the possible late complications resulting from adhesions.[34] The risk of intestinal obstruction should be discussed with patients and families during consent for radiotherapy and surgery, as well as throughout treatment. Furthermore, survivors of childhood cancer should be followed regularly to reinforce the signs and symptoms of intestinal obstruction.

There are several important limitations to this study. The primary outcome, IOS, was self-reported and without medical record confirmation. However, previous studies have validated the use of self-reports in the CCSS, especially for complications with clear diagnostic criteria.[5,35] Results from the CCSS cohort only address risk of IOS as a late event among 5-year survivors because IOS was not recorded as a recurrent outcome variable. Thus, patients who experienced IOS within the first 5 years after diagnosis were necessarily excluded from the analysis of late IOS. Given these limitations, we were unable to assess the relationship between early and late IOS. However, to mitigate these missing data, we provided the prevalence of early IOS within 5 years of diagnosis. Finally, the etiology of intestinal obstruction (eg, adhesions, stricture, internal hernia) was not ascertained.

In conclusion, survivors of childhood cancer are at increased long-term risk of IOS, including 5.8% of patients with abdominal or

pelvic tumors at 35 years after diagnosis. The risk of IOS extends for decades beyond cancer diagnosis, implying the need for long-term vigilance, especially among survivors with abdominal or pelvic tumors and survivors who have undergone treatment with abdominal or pelvic surgery or radiotherapy. Widespread awareness of the signs and symptoms of IOS will facilitate timely presentation and effective management of this complication. Although prevention of IOS is not currently possible, education of survivors of cancer, their families, and their health care providers is critical.

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Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

cumulative incidence: a statistical measure of an event of interest (eg, relapse, death, second malignant neoplasm, a specific disease) occurring in a specified period of time in the population at risk. It is calculated using the formula: (number of new cases of the event of interest)/(total population at risk).

overall survival: the duration between random assignment and death.

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Intestinal Obstruction in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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Appendix

Table A1. Information About Missing Demographic and Treatment Characteristics of 12,316 Survivors of Childhood Cancer and 4,023 Siblings

Characteristic	No. (%)*		
	Abdominopelvic Tumor (n = 2,002)	No Abdominopelvic Tumor (n = 10,314)	Siblings (n = 4,023)
Primary cancer diagnosis	0 (0)	0 (0)	
No of abdominal/pelvic surgeries†	278 (14)	1,235 (12)	
Received chemotherapy†	277 (14)	1,222 (12)	
Alkylating agent CED†	363 (18)	2,094 (20)	
Platinum agent score†	302 (15)	1,389 (13)	
Dose to abdomen/pelvis from all radiotherapy†	298 (15)	1,401 (14)	
Sex	0 (0)	0 (0)	0 (0)
Race/ethnicity	0 (0)	0 (0)	0 (0)
Year of diagnosis	0 (0)	0 (0)	
Age at diagnosis	0 (0)	0 (0)	

Abbreviation: CED, cyclophosphamide equivalent dose.
*Percentages are column percentages, where the denominator is the total number of patients.
†Occurring within 5 years of childhood cancer diagnosis.

Table A2. Multivariable Analysis of Factors Associated With Late IOS Among Survivors With and Without Abdominopelvic Tumors (primary cancer diagnosis excluded from model)

Factor	Abdominopelvic Tumor		No Abdominopelvic Tumor	
	Adjusted Rate Ratio (95% CI)*	*P*	Adjusted Rate Ratio (95% CI)*	*P*
Abdominal/pelvic surgery†				
No	1.0		1.0	
Yes	0.9 (0.5 to 1.4)	.54	4.5 (2.4 to 8.7)	< .001
Chemotherapy†				
No	1.0		1.0	
Yes	0.9 (0.4 to 2.0)	.74	0.9 (0.5 to 1.5)	.60
Dose to abdomen/pelvis from all radiotherapy, Gy†				
0	1.0		1.0	
< 10			3.2 (0.4 to 23.8)	.25
10-19	1.7 (0.7 to 3.8)	.21		
20-29	2.2 (1.2 to 4.2)	.017	0.5 (0.1 to 3.7)	.50
30-39	2.6 (1.2 to 5.4)	.013	1.6 (0.6 to 4.3)	.37
40-49	4.4 (1.9 to 9.8)	< .001	2.6 (1.0 to 6.6)	.042
≥ 50	4.3 (1.2 to 15.8)	.029	9.7 (3.9 to 24.2)	< .001
Sex				
Male	1.0		1.0	
Female	1.0 (0.6 to 1.6)	.95	1.0 (0.6 to 1.6)	.88
Race/ethnicity				
Non-Hispanic white	1.0		1.0	
Non-Hispanic black	0.9 (0.3 to 2.6)	.94	0.7 (0.1 to 4.9)	.70
Hispanic	0.6 (0.1 to 2.4)	.44	0.3 (0.0 to 2.5)	.30
Other	1.2 (0.3 to 4.7)	.83	0.6 (0.1 to 4.1)	.58
Age at diagnosis, years				
0-3	1.0		1.0	
4-9	1.6 (1.0 to 2.6)	.07	0.6 (0.3 to 1.4)	.25
10-14	0.7 (0.2 to 2.1)	.53	0.4 (0.1 to 1.0)	.054
15-20	0.8 (0.2 to 3.2)	.72	0.7 (0.3 to 1.9)	.53
Year of diagnosis				
1970-1974	1.0		1.0	
1975-1979	1.3 (0.7 to 2.2)	.44	1.4 (0.6 to 3.0)	.40
1980-1986	1.1 (0.6 to 2.1)	.77	1.7 (0.8 to 3.7)	.15

Abbreviation: IOS, intestinal obstruction requiring surgery.
*Adjusted for the variables in the table in addition to age during follow-up as natural cubic splines.
†Occurring within 5 years of childhood cancer diagnosis.